PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/44 — A1

(11) International Publication Number: WO 98/55122

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/EP98/03478

(22) International Filing Date: 2 June 1998 (02.06.98)

(30) Priority Data:

9711683.4	5 June 1997 (05.06.97)	GB
9712851.6	18 June 1997 (18.06.97)	GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITION COMPRISING 5-[4-[2-(N-METHYL-N-2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

(57) Abstract

A pharmaceutical composition comprising Compound (I), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor, the use of such a composition in medicine, processes for the preparation of such a composition and intermediate composition useful in such a process.

Particular compositions comprise 2 to 4mg of Compound (I) in a pharmaceutically acceptable form.

Particular compositions comprise 4 to 8mg of Compound (I) in a pharmaceutically acceptable form.

Particular compositions comprise 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

One composition comprises 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprise 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprise 8 mg of Compound (I) in a pharmaceutically acceptable form.

Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

Compound (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term 'Compound (I)' as individual tautomeric forms or as mixtures thereof.

Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

When used herein the term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular those requiring the regulation of appetite and food intake, such as disorders associated with under-eating, for example anorexia nervosa and disorders associated with over-eating, for example obesity and anorexia bulimia. Additional conditions associated with diabetes mellitus itself include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

As used herein the term concentrate with respect to Compound (I) in a pharmaceutically acceptable form means a proportionate amount of Compound (I) in a pharmaceutically acceptable form greater than that present in an administerable composition.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts and % weight amounts, of 'Compound (I) in a pharmaceutically acceptable form', the scalar amount referred to is made in respect of Compound (I) *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type II diabetes.

In a further aspect, the invention provides a process for preparing a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, and a pharmaceutically acceptable carrier therefor, which process comprises admixing 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and the pharmaceutically acceptable carrier and optionally thereafter formulating the composition produced into an administerable form.

As indicated above the invention also provides a further process for preparing a pharmaceutical composition comprising Compound (I) in a pharmaceutically acceptable form which is particularly suitable for preparing a range of unit dosage forms of Compound (I). Accordingly, the invention further provides a process for preparing a pharmaceutical composition of Compound (I) in a pharmaceutically acceptable form and a pharmaceutically acceptable carrier, which process comprises:

(i) preparing a first composition comprising Compound (I) in a pharmaceutically acceptable form and a first pharmaceutically acceptable carrier;

(ii) admixing the first composition with a second pharmaceutically acceptable carrier to provide the required composition of Compound (I) and optionally thereafter formulating the composition produced into an administerable form.

A preferred administerable form of the pharmaceutical composition of Compound (I) is a unit dose composition.

Unless otherwise specified, suitable unit doses comprise up to 12 mg, such as 1 to 12 mg, of Compound (I) in a pharmaceutically acceptable form.

Other unit doses include those mentioned herein.

A key component of the last above mentioned process is the first composition. Accordingly, the present invention also provides a composition for use as a first composition in a process for preparing a unit dose of Compound (I) in a pharmaceutically acceptable form.

The invention also provides a composition comprising Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier, characterised in that the composition is a pharmaceutically acceptable, pre-administration composition.

A suitable pharmaceutically acceptable, pre-administration composition is a concentrate, preferably a granular concentrate, of Compound (I) in a pharmaceutically acceptable form. The granular concentrate is particularly well adapted to be diluted to provide a composition for administration, preferably a tablet.

In a further aspect the invention provides a composition comprising Compound (I) in a pharmaceutically acceptable form and a pharmaceutically acceptable carrier, characterised in that the composition is a concentrate of Compound (I) in a pharmaceutically acceptable form, adapted to be diluted so as to provide a composition for administration.

Suitably, the first composition, pre-administration composition or dilutable composition (hereinafter referred to for convenience as 'the first composition') contains up to 50% by weight, for example an amount in the range of from 2 to 50% by weight, of Compound (I) in a pharmaceutically acceptable form.

Favourably, the first composition contains an amount of Compound (I) in a pharmaceutically acceptable form in the range of from 5 to 20% by weight, in particular 5%, 10% or 15% by weight, for example 10% by weight.

The processes of the invention can provide pharmaceutical compositions of Compound (I) in any conventionally administerable form, including orally or parenterally adminsterable forms. They are particularly well adapted for preparing orally administrable forms, especially tablet forms of Compound (I) in a pharmaceutically acceptable form.

The first pharmaceutically acceptable carrier can comprise any conventional pharmaceutically acceptable carrier comprising conventional pharmaceutically acceptable excipients, including those disclosed in the reference texts mentioned below. However, as it is not essential that the first pharmaceutically acceptable carrier is in an administerable form, then it need not contain excipients solely associated with administration. For example the first pharmaceutically acceptable carrier need not contain a lubricant.

The second pharmaceutically acceptable carrier includes any conventional pharmaceutically acceptable carrier comprising any conventional pharmaceutically acceptable excipient, including disintegrants, diluents and lubricants, including those disclosed in the reference texts mentioned below.

One particular first composition comprises Compound (I) in a pharmaceutically acceptable form, a disintegrant, a binder and a diluent.

A suitable disintegrant is sodium starch glycollate.

A suitable binder is a methyl cellulose binder, such as hydroxypropyl methylcellulose 2910.

Suitable diluents include cellulose, for example a microcrystalline cellulose, and lactose monohydrate.

A suitable lubricant is magnesium stearate.

We have found that a particularly advantageous first composition contains Compound (I) in a pharmaceutically acceptable form, sodium starch glycollate, hydroxypropyl methylcellulose 2910, microcrystalline cellulose and lactose

monohydrate, especially when in a granular form. This granular form has been found to be particularly stable.

When the first composition contains about 10% by weight of Compound (I) in a pharmaceutically acceptable form, it is readily dilutable to give unit dose compositions comprising in the range of between 2 to 12 mg , especially 2 to 8 mg, 2 to 4mg, 4 to 8 mg and 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

The preparation of the first composition is suitably carried using any conventional method appropriate to the nature of the said first composition, for example wet granulation methods provide the first composition in granular form.

Methods for formulating the compositions of the invention into administerable forms include conventional formulation methods as disclosed in the reference texts cited herein, including tabletting methods.

The administerable compositions of the invention are preferably adapted for oral administration. However, they may also be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The administerable compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

Unless otherwise prescribed, compositions of the invention are preferably in unit dosage form in an amount appropriate for the relevant daily dosage, suitable unit dosages comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I) in a pharmaceutically acceptable form.

The solid compositions for example the oral compositions may be prepared by conventional methods of blending, filling or tabletting. As required repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods

well known in normal pharmaceutical practice, in particular with an aqueous film coating.

Liquid compositions, for example oral liquid compositions, may be in the form of emulsions, syrups, or elixirs, or they may be in a dry product form to be reconstituted with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Parenteral compositions, including parenteral administration compositions for example unit dosage compositions, comprise the active compound and a sterile vehicle, and, depending upon the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions for parenteral administration the composition of the invention may be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the active compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Unless otherwise specified the compositions of the invention may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions of the invention may be prepared and formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The present invention also provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

In particular, the present invention provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, for use in the treatment of diabetes mellitus, especially Type II diabetes, and conditions associated with diabetes mellitus..

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

Accordingly, in a further aspect the invention provides a method for treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus, in a mammal such as a human, which method comprises administering per day 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, to a mammal in need thereof.

Particularly, the method comprises the administration of 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

Particular dosages are 2mg/day, 4mg/day, including 2mg twice per day, and 8 mg/day, including 4mg twice per day.

Particularly, the method comprises the administration of 2 to 4mg of Compound (I) in a pharmaceutically acceptable form.

Particularly, the method comprises the administration of 4 to 8mg of Compound (I) in a pharmaceutically acceptable form.

Particularly, the method comprises the administration of 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 8 mg of Compound (I) in a pharmaceutically acceptable form.

A range of 2 to 4mg includes a range of 2.1 to 4, 2.2 to 4, 2.3 to 4, 2.4 to 4, 2.5 to 4, 2.6 to 4, 2.7 to 4, 2.8 to 4, 2.9 to 4 or 3 to 4mg.

A range of 4 to 8mg includes a range of 4.1 to 8, 4.2 to 8, 4.3 to 8, 4.4 to 8, 4.5 to 8, 4.6 to 8, 4.7 to 8, 4.8 to 8, 4.9 to 8, 5 to 8, 6 to 8 or 7 to 8mg.

A range of 8 to 12 mg includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6 to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to 12mg.

No adverse toxicological effects have been established for the compositions or methods of the invention in the abovementioned dosage ranges.

The following examples illustrate the invention but do not limit it in any way.

Example 1: Concentrate Preparation
Approximately two thirds of the lactose monohydrate is passed through a suitable screen and blended with the milled maleate salt of Compound (I).
Sodium starch glycollate, hydoxypropyl methylcellulose, microcrystalline cellulose and the remaining lactose are passed through a suitable screen and added to the mixture. Blending is then continued. The resulting mixture is then wet granulated with purified water. The wet granules are then screened, dried on a fluid bed drier and the dried granules are passed through a further screen and finally homogenised.

% COMPOSITION OF GRANULAR CONCENTRATE

Ingredient	**Quantity (%)**
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydoxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

Example 2: Formulation of the concentrate into tablets.

The granules from Example 1 are placed into a tumble blender. Approximately two thirds of the lactose is screened and added to the blender. The microcrystalline cellulose, sodium starch glycollate, magnesium stearate and remaining lactose are screened and added to the blender and the mixture blended together. The resulting mix is then compressed on a rotary tablet press to a target weight of 150mg for the 1, 2 and 4mg tablets and to a target weight of 300mg for the 8mg tablets.
The tablet cores are then transferred to a tablet coating machine, pre-warmed with warm air (approximately 65°C) and film coated until the tablet weight has increased by 2.0% to 3.5%.

	Quantity (mg per Tablet)			
Tablet Strength	**1.0mg**	**2.0mg**	**4.0mg**	**8.0mg**
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose	27.85	25.85	21.85	43.70
Lactose monohydrate	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Aqueous film coating material	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

COMPOSITION COMPRISING 5-[4-[2-(N-METHYL-N-2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

This invention relates to a composition, in particular to a pharmaceutical composition, and to the use of such a composition in medicine, to processes for the preparation of such a composition and to a composition useful in such a process.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). International Patent Application, publication number WO94/05659 discloses certain salts of Compound (I), including the maleate salt at Example 1 thereof.

It is now surprisingly indicated that a discrete and particular daily dosage of Compound (I) provides an especially beneficial effect on glycaemic control and is therefore particularly useful for treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

We have also discovered a new and advantageous method for preparing pharmaceutical compositions, especially unit dosage compositions, containing Compound (I). The new method involves the preparation of a pre-administration concentrate of Compound (I) which thereafter is formulated into the required unit dose in an efficient and economical manner. The new process is particularly advantageous for the preparation of tablets of Compound (I).

Accordingly, in a first aspect the present invention provides a pharmaceutical composition, suitably in unit dosage form, comprising Compound (I), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor.

Suitable pharmaceutically acceptable forms of Compound (I) include pharmaceutically acceptable salted forms and pharmaceutically acceptable solvated forms, including pharmaceutically acceptable solvated forms of pharmaceutically acceptable salts.

Suitable compositions comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I) in a pharmaceutically acceptable form.

ENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
KR/P31824		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 03478	02/06/1998	05/06/1997
Applicant		
SMITHKLINE BEECHAM P.L.C. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application.
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   COMPOSITION COMPRISING 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03478

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	"ROSIGLITAZONE SMITHKLINE BEECHAM CLINICAL DATA" STN FILE SUPPLIER: DRUGNL: ACCESSION NUMBER 1391 & R&D FOCUS DRUG NEWS, 27 April 1998, XP002082989 see the whole document ---	1-4,6-9
P,X	"THE PINK SHEET" DIALOG FILE SUPPLIER: FILE 187:F-D-C REPORTS; ACCESSION NUMBER 600160005, vol. 60, no. Issue 16, 20 April 1998, XP002082978 see the whole document --- -/--	1,3,4, 7-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1998	17/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Hoff, P

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 98/03478

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 02159 A (POSTE GEORGE HENRY ;SMITH STEPHEN ALISTAIR (GB); SMITHKLINE BEECHA) 22 January 1998 see page 14, line 4 - line 10 see page 19, line 1 - line 16; claims; examples	1,4,8-16
X	WO 95 21608 A (SMITHKLINE BEECHAM PLC ;BUCKINGHAM ROBIN EDWIN (GB)) 17 August 1995 see page 4, line 28 - page 5, line 2 see page 7, line 29 - page 8, line 33; claims; examples	1,4,8-16
X	EP 0 796 618 A (SANKYO CO) 24 September 1997 see page 8, line 28 - line 30 see page 8, line 58 - page 9, line 42	10-17
X	WO 97 05875 A (WARNER LAMBERT CO ;WHITCOMB RANDALL W (US)) 20 February 1997 see page 20, line 19 - line 33 see page 24, line 24 - page 27, line 8	10-19,21
X	WO 97 18811 A (WARNER LAMBERT CO ;LOCKWOOD DEAN (US)) 29 May 1997 see page 18, line 15 - line 29 see page 21, line 16 - page 23, line 34	10-19,21
Y	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 cited in the application see page 9, line 9 - page 10, line 13; claims; example 30	1-21
Y	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 cited in the application see the whole document	1-21
Y	"R&D FOCUS DRUG NEWS " DIALOG FILE SUPPLIER: FILE 445 R&D FOCUS; ACCESSION NUMBERS 16402 AND 14818, 5 May 1997 - 10 March 1997, XP002082979 see the whole document	1-21

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BERGER J ET AL: "THIAZOLIDINEDIONES PRODUCE A CONFORMATIONAL CHANGE IN PEROXISOMAL PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA: BINDING AND ACTIVATION CORRELATE WITH ANTIDIABETIC ACTIONS IN DB/DB MICE" ENDOCRINOLOGY, vol. 137, no. 10, October 1996, pages 4189-4195, XP000613643 -----	1-21

INTERNATIONAL SEARCH REPORT

Inform on patent family members

Inte nal Application No
PC.. _P 98/03478

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WO 9802159 A	22-01-1998	AU 3552697 A	09-02-1998
WO 9521608 A	17-08-1995	AP 553 A	06-11-1996
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INTERNATIONAL SEARCH REPORT

Inform on patent family members

Inte nal Application No
PC EP 98/03478

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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27-04-1998; p. 1

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SO R&D Focus Drug News (27 Apr 1998).
WC 267
TX US and European submissions for approval of ***rosiglitazone*** (***AVANDIA***), SmithKline Beecham's insulin sensitizer, will take place during the next twelve months, according to J-P Garnier, Chief Operating Officer and President, speaking at the company's Research & Development Review Meeting, 16 April 1998, London, UK. Around 5000 patients are being enrolled in blinded, phase III trials of the product, scheduled to involve between 6 and 12 months of treatment. The studies are investigating ***rosiglitazone*** 's potential both as a first-line monotherapy, and in combination with conventional therapies, such as sulfonylureas, metformin, or insulin.

Clinical data were reported by SmithKline Beecham at the meeting, highlighting both ***rosiglitazone*** 's safety and tolerability profile and its efficacy in patients. ***Rosiglitazone*** was found to be safe and effective when given as a once daily monotherapy, and was not influenced by food. The product's tolerability was equivalent to placebo, and no clinically important drug interactions have been detected. No cases of jaundice or serious hepatic abnormalities have been seen in clinical trials to date. Monotherapy with 4 or 8 mg/d ***rosiglitazone*** over six months resulted in mean reductions in HbA1c from baseline of 0.3% and 0.5%, respectively, compared with an increase of 0.9% from baseline for placebo. Clinical studies of troglitazone, in comparison, found increases in HbA1c from baseline of around 0.8% and 0.4% at doses of 400 or 600 mg/d, respectively. The two agents have not been compared directly, however. After eight weeks of treatment with ***rosiglitazone*** 4 and 8 mg/d FPG was decreased from baseline by 17 mg/dL and 32 mg/dL respectively, compared with an increase from baseline of 7 mg/dL for placebo.

CN ***rosiglitazone*** ; ***BRL*** ***49653*** ; ***AVANDIA***
RN ***122320-73-4***
CC A10B Oral Antidiabetics
CO SmithKline Beecham
DSTA clinical data.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
KR/P31824		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/03478	02/06/1998	05/06/1997
International Patent Classification (IPC) or national classification and IPC A61K31/44		
Applicant SMITHKLINE BEECHAM P.L.C. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/12/1998	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Brunnauer, H

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/03478

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-21 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings. sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12, 17-19, 21
	No:	Claims	13-16, 20
Inventive step (IS)	Yes:	Claims	-----
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	-----

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V

1. Reference is made to the following documents:

   D1: WO 95 21608 A
   D2: EP 0 796 618 A
   D3: WO 97 05875 A
   D4: WO 97 18811 A
   D5: EP 0 306 228 A
   D6: WO 94 05659 A
   D7: Endocrinology, vol. 137, no. 10, pages 4189-4195, 1996

2. Summary of the cited prior art documents D1 - D7

   Document D1 (abstract; page 4, line 28-29 and page 5, line 1) discloses a method for treatment of renal diseases by means of administering i.a. the insulin sensitiser 5-{4-{2-(N-methyl-N-(2-pyridyl)amino)ethoxy} benzyl} thiazolidine-2,4-dione (compound I), or the maleic acid salt thereof. Said compound (I) is admixed with a suitable carrier, including microcristalline cellulose and sodium starch glycollate (page 8, line 17-19). The resulting composition will be formulated in an unit dose form, i.e. tablets, containing the active ingredient in an amount of from 0,1 to 1000 mg (page 8, line 9, 20-23).

   Document D2 (abstract) refers to diverse insulin sensitizer containing compounds, which are useful for the treatment of pancreatitis. Examples of such compounds include 5-{4-{2-(N-methyl-N-(2-pyridyl)amino)ethoxy} benzyl} thiazolidine-2,4-dione, compound (I) (page 8, line 28-39). It is referred to said compounds as being administered by various routes, i.e. by the oral route in form of tablets. Suitable carriers may be admixed, i.a. lactose, starch, crystalline cellulose or methyl cellulose. The amount of the active ingredient may be selected over a wide range, in general from 1 to 70% by weight compared to the whole composition (page 9, line 3, 11-14, 36-37).

   Document D3 (abstract; page 11, line 31-32) is addressed to compounds comprising i.a. active substances recruited from 5-{4-(chromoanalkoxy) benzyl}

thiazolidene derivatives for treating patients suffering from noninsulin-dependent diabetes mellitus. it is referred to i.a. solid dosage forms suitable for oral administration, i.e. tablets, comprising suitable carriers such as lactose, starch or methylcellulose (page 25, line 5-19). The quantity of active component in a unit dosage preparation may be varied or adjusted from 0,1 mg to 600 mg according to the particular application and the potency of the active component (page 26, line 29-31). Document D4 (abstract; page 9, line 34-35 - page 10, line 1) is also addressed to compounds comprising i.a. active substances recruited from 5-(4-chromoanalkoxy) benzyl) thiazolidene derivatives, useful for treating myotonic dystrophy.

Document D5 discloses i.a. the substance 5-(4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy) benzyl) thiazolidine-2,4-dione, which is described as being useful for the treatment of hyperglycemia (page 38, example 30 and page 9, line 11). Accordingly, suitable compositions may be formed, i.a. tablets in unit dose form, which contain an amount of the active ingredient in the range from 0,1 to 1000 mg and more especially 0,1 to 250 mg. Typical carriers include i.a. microcrystalline cellulose, sodium starch glycollate (page 9, line 29-40). Further on, it is suggested to apply corresponding pharmaceutical compositions one to six times a day in a manner such that the total daily dose for a 70 kg adult will be generally in the range of from about 1 to 1500 mg (page 9, line 56-58).

Document D6 refers to i.a. 5-(4-(2-(N-methyl-N-(2-pyridyl)amino) ethoxy) benzyl) thiazolidine-2,4-dione, maleic acid salt (page 8, examples 1 and 2) for use in the treatment of hyperglycemia, comprised in suitable unit dosage form, i.e. tablets, in an amount from 0,1-1000 mg, whereby the carries include i.a. microcrystalline cellulose and sodium starch glycollate (page 6, line 24-35; claims 12 and 13, pages 10-11).

Document D7 (abstract) refers to the insulin-sensitizing effect of some thiazolidinediones, i.a. 5-(4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy) benzyl) thiazolidine-2,4-dione, in obese hyperglycemic mice. Glucose levels were normalized at doses of 1,7 and 30 mg/kg (page 4192, right column, "discussion").

3. Novelty according to Article 33(2) PCT

Claims 13-16 are not novel in the sense of article 33(2), since documents D1- D2 and D5-D6 already disclose compositions comprising compound I and pharmaceutically acceptable carriers (see also section VIII of this report).

Claim 20 is not novel over documents D1-D3 and D5 - D6, which already discloses pharmaceutically acceptable carriers, i.a. sodium starch glycollate (D1, D5, D6) and microcrystalline cellulose (D1, D2, D5, D6).

Claims 1-12 and 17-19 and 21 are novel in the sense of Article 33(2) PCT, since particular features are not disclosed in above cited prior art documents D1-D7.

4. Inventive step according to Article 33(3) PCT

4.1 Claims 1-8, 9 and 11-12

Claims 1-8, 9 and 11-12 are not regarded as involving an inventive step in accordance with Article 33(3) PCT for the following reasons.

Documents D1 - D7 refer to the therapeutical use of diverse, orally administered thiazolodine-derivatives, in particular to compound I, the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy] benzyl] thiazolidine-2,4-dione (D1-D2, D5-D7) as being useful for the treatment of hyperglycemia (D5-D7).

The subject-matter of claims 1-8 differs therefrom in that said compositions are not disclosed as containing the active ingredient in the particular dose range, as claimed. The suggested dose ranges per unit dosage varies according to the prior art from counting 0,1-1000 mg (D1, D5, D6) or 0,1-600 mg (D3). D7 refers to active doses of 1,7 and 30 mg/kg of compound I.
However, the skilled person would routineously try different dose ranges in order to reach at the known effect.

The corresponding claims 9, 11 and 12 with reference to the process of preparing said compositions comprising 2 to 12 mg of compound I are equally not regarded

as involving an inventive step for the same reasons as presented above.

4.2 Claims 10, 21

The preparation of a first composition, comprising compound I and a first carrier, prior to admix it with a second carrier (claim 10) is regarded as a common routine measure for persons skilled in pharmaceutical production processes and therefore regarded as lacking an inventive step. It is common practise to produce intermediate bulk products prior to prepare final admixtures, ready for being further processed, i.e. in form of tablets.

Subject-matter of claim 21 is not regarded as involving an inventive step, since the preparation of said composition in granular form is regarded as an obvious modification on a routine basis for the person skilled in the art.

4.3 Claims 17-19

Subject-matter of claims 17-19 do not meet the provisions of Article 33(3) PCT, since the preparation of said composition by means of adding the active substance in particular weight ranges is regarded as an optimisation in respect of amounts only.

Section VI

Following patent application, classified as p, x- document in the International Search Report, is cited:

WO 98 02159 A, published 22 January 1998, filed 14 July 1997 with the priority date of 12 July 1996.

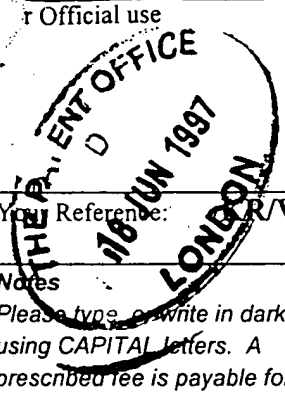
Section VII

Contrary to the requirements of rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 and D7 is not mentioned in the description, nor are these documents identified therein.

Section VIII

Claims 13-16 are not clear in the sense of Article 6 PCT, because the additional feature "for use as a first composition" or "..pre-adminstration composition.." does not characterize the claimed composition per se. It only indicates that the composition is further processed prior to use. The terms "..first composition.." (claims 13, 15) and "...pre-administration composition..." (claim 14) as well as "..a concentrate of compound I.." (claim 16) are therefore not regarded as being distinguishing features (see also paragraph 2 of this written opinion).

r Official use



18 JUN 1997

19JUN97 E282992-1 D02029
P01/7700 25.00 - 9712851.6

Your Reference: KR/VB/P31827

9712851.6

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-483 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

The Patent Office

Request for grant of a Patent

Form 1/77 **Patents Act 1977**

❶ Title of invention

1 Please give the title of the invention COMPOSITION

❷ Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:
Corporate Name SMITHKLINE BEECHAM PLC

Country (*and State of incorporation, if appropriate*) UNITED KINGDOM

❷ *Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.*

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please given the following details:

Address: NEW HORIZONS COURT
BRENTFORD
MIDDLESEX

UK postcode (*if applicable*) TW8 9EP

Country ENGLAND

ADP number (*if known*) 5100974002

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

2d, 2e and 2f: *If there are further applicants please provide details on a separate sheet of paper*

❑ Second applicant *(if any)*

2d If you are applying as a corporate body please give:
Corporate Name

Country *(and State of Incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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Forenames:

2f **In all cases,** please give the following details:

Address:

UK postcode *(if applicable)*
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ADP number *(if known)*

❸ *An address for service in the United Kingdom must be supplied*

Please mark correct box.

❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ ➲ *go to 3b*

❶ ***please give details below***

Agent's name **RUTTER K**
Agent's address: CORPORATE INTELLECTUAL PROPERTY
SMITHKLINE BEECHAM PLC
2 NEW HORIZONS COURT
GREAT WEST ROAD
BRENTFORD
MIDDLESEX

Postcode TW8 9EP 70522770001
Agent's ADP number

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name:

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Postcode

Daytime telephone number *(if available)*

ADP number *(if known)*

4. Agent's or applicant's reference number *(if applicable)* — **Reference number** P31827

5 Claiming an earlier application date

5. Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ *go to 6*

please give details below

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number

Please give the date in all number format, for example, 31/05/90 for 31 May 1990

6. If you are declaring priority from previous application(s), please give:

Country of Filing	Priority application number *(if known)*	Filing Date *(day, month, year)*

❼

- a··· applicant is not an inventor
- b. ... is an inventor who is not
- an applicant, or
- any applicant is a corporate body.

❼ Inventorship

7. Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐ No ☒ ➲ ***A Statement of Inventorship on Patents form 7/77 will need to be filed (see Rule 15).).***

❽ *Please supply duplicates of claim(s), abstract, description and drawings).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application

Continuation sheets for this Patents Form 1/77 ☐

2
5

Claim(s)	**0**	Description	**7**
Abstract	**0**	Drawing(s)	**0**

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)* ☐

Translation(s) of Priority documents *(please state how many)* ☐

Patents Form 7/77 - Statement of Inventorship and Right to Grant ☐

Patents Form 9/77 - Preliminary Examination Report ☐

Patents Form 10/77 - Request for Substantive Examination ☐

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/We request the grant of a patent on the basis of this application.

Please sign here á

Signed _____ Date: 18 JUNE 1997

K RUTTER (day month year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either;

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COMPOSITION

This invention relates to a composition, in particular to a pharmaceutical composition, to processes for the preparation of such a composition and to the use of such a composition in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.

It is now surprisingly indicated that a discrete and particular daily dosage of Compound (I) provides a disproportionately beneficial effect on glycaemic control and is therefore particularly useful for treatment and/or prophylaxis of diabetes mellitus, especially Type II diabetes, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, in one aspect the present invention provides a pharmaceutical composition comprising Compound (I), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor.

A suitable pharmaceutically acceptable form of Compound (I) includes a pharmaceutically acceptable salted form and/or a pharmaceutically acceptable solvated form.

Particular compositions comprise 2 to 4mg of Compound (I) in a pharmaceutically acceptable form.

Particular compositions comprise 4 to 8mg, such as greater than 4 for example 4.1, to 8 mg, of Compound (I) in a pharmaceutically acceptable form.

Particular compositions comprise 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

One composition comprises 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprises 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprises 8 mg of Compound (I) in a pharmaceutically acceptable form.

Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Conditions associated with diabetes include hyperglycaemia and insulin resistance, especially acquired insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

In one aspect, the invention provides a process for preparing a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, and a pharmaceutically acceptable carrier therefor, which process admixing 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and the pharmaceutically acceptable carrier.

The composition of the invention is preferably adapted for oral administration. However, it may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The composition of the invention is preferably in a unit dosage form in an amount appropriate for the relevant daily dosage, suitable unit dosages comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I) in a pharmaceutically acceptable form.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a

preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the Compound (I)s suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions of the invention may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions of the invention may be prepared and formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The present invention also provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

In particular, the present invention provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, for use in the treatment and/or prophylaxis of diabetes mellitus, especially Type II diabetes, conditions associated with diabetes mellitus and certain complication thereof.

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

Accordingly, in a further aspect the invention provides a method for the treatment and/or prophylaxis of diabetes mellitus, especially Type II diabetes, conditions associated with diabetes mellitus and certain complication thereof, in a mammal such as a human, which method comprises administering per day 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, to a mammal in need thereof.

Particularly, the method comprises the administration of 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

Particularly, the method comprises the administration of 2 to 4mg of Compound (I) in a pharmaceutically acceptable form.

Particularly, the method comprises the administration of 4 to 8mg, such as greater than 4 for example 4.1, to 8 mg, of Compound (I) in a pharmaceutically acceptable form.

Particularly, the method comprises the administration of 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 8 mg of Compound (I) in a pharmaceutically acceptable form.

No adverse toxicological effects have been established for the compositions or methods of the invention in the abovementioned dosage ranges.

The following example illustrates the invention but does not limit it in any way.

Example

Preparation of Concentrate: Tabletting concentrate was prepared using the following materials

Ingredient	Quantity (%)
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydoxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose (Avicel PH102)	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

The concentrate was then formulated into tablets using the following:

	Quantity (mg per Tablet)			
Tablet Strength	**1.0mg**	**2.0mg**	**4.0mg**	**8.0mg**
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose (Avicel PH102)	27.85	25.85	21.85	43.70
Lactose monohydrate, (Pharmatose DCL15),	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Opadry	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

For Official use

- 5 JUN 1997

06JUN97 E279852-1 D02029
P01/7700 25.00 9711683.4

Reference: KR/jb/P31824

9711683.4

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-483 4700).

The Patent Office

Request for grant of a Patent

Form 1/77 **Patents Act 1977**

9711683.4

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

❶ Title of invention

1 Please give the title of the invention: Composition

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

THE PATENT OFFICE
- 5 JUN 1997
LONDON

❷ Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:
Corporate Name: SMITHKLINE BEECHAM PLC

Country (*and State of incorporation, if appropriate*): UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please given the following details:

Address: NEW HORIZONS COURT
BRENTFORD
MIDDLESEX

UK postcode (*if applicable*): TW8 9EP

Country: ENGLAND

ADP number (*if known*)

5809974002

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper

Second applicant *(if any)*

2d If you are applying as a corporate body please give:
Corporate Name

Country *(and State of Incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname:

Forenames:

2f **In all cases**, please give the following details:

Address:

UK postcode *(if applicable)*
Country
ADP number *(if known)*

❸ *An address for service in the United Kingdom must be supplied*

Please mark correct box.

❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ ➲ *go to 3b*

please give details below

Agent's name **Rutter K**
Agent's address: CORPORATE INTELLECTUAL PROPERTY
SMITHKLINE BEECHAM PLC
2 NEW HORIZONS COURT
BRENTFORD
MIDDLESEX

Postcode TW8 9EP
Agent's ADP number 10522771001

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name:

Address

Postcode

Daytime telephone number *(if available)*

ADP number *(if known)*

❹ R ence number P31824

4. Agent's or applicant's reference number *(if applicable)*

❺ Claiming an earlier application date

5. Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➲ ***go to 6***

please give details below

☐ number of earlier application or patent number

☐ **filing date** *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number

Please give the date in all number format, for example, 31/05/90 for 31 May 1990

6. If you are declaring priority from previous application(s), please give:

Country of Filing	Priority application number *(if known)*	Filing Date *(day, month, year)*

❼

•an applicant is not an inventor
•there is an inventor who is not
•an applicant, or
•any applicant is a corporate body.

Inventorship

7. Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐ No ☒ ➲ ***A Statement of Inventorship on Patents form 7/77 will need to be filed (see Rule 15).).***

❽ ***Please supply duplicates of claim(s), abstract, description and drawings).***

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application

Continuation sheets for this Patents Form 1/77 ☐

Claim(s) 2 Description 7

Abstract 1 Drawing(s)

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)* ☐

Translation(s) of Priority documents *(please state how many)* ☐

Patents Form 7/77 - Statement of Inventorship and Right to Grant ☐

Patents Form 9/77 - Preliminary Examination Report ☐

Patents Form 10/77 - Request for Substantive Examination ☐

❾ ***You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.***

❾ Request

I/We request the grant of a patent on the basis of this application.

Please sign here á

Signed K Rutter Date: 05 (day) 06 (month) 1997 (year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either;

☐ *The Comptroller*
The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

or

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The Patent Office
25 Southampton Buildings
London
WC2A 1AY

COMPOSITION

This invention relates to a composition, in particular to a pharmaceutical composition, to processes for the preparation of such a composition and to the use of such a composition in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.

It has now been discovered that a discrete and particular pharmaceutical composition comprising Compound (I) is particularly useful for treatment and/or prophylaxis of conditions associated with diabetes mellitus especially Type II diabetes and hyperglycaemia and certain complications thereof.

This composition is also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia and hypertension and of cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

Accordingly, in one aspect the present invention provides a pharmaceutical composition comprising Compound (I), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor.

A suitable pharmaceutically acceptable form of Compound (I) includes a pharmaceutically acceptable salted form and/or a pharmaceutically acceptable solvated form.

Particular compositions comprise 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

One composition comprises 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprises 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferred compositions comprises 8 mg of Compound (I) in a pharmaceutically acceptable form.

Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compund (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compounds contains a chiral carbon atom, and hence they can exist in one or more stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, especially inherited insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

In one aspect, the invention provides a process for preparing a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, and a pharmaceutically acceptable carrier therefor, which process admixing 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and the pharmaceutically acceptable carrier.

The composition of the invention is preferably adapted for oral administration. However, it may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The composition of the invention is preferably in unit dosage form, said unit dosage comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I) in a pharmaceutically acceptable form.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the Compound (I)s suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle.

Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions of the invention may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions of the invention may be prepared and formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The present invention also provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

In particular, the present invention provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, for use in the treatment and/or prophylaxis of diabetes mellitus especially Type II diabetes and hyperglycaemia and certain complications thereof, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and for treating certain eating disorders.

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

Accordingly, in a further aspect the invention provides a method for the treatment and/or prophylaxis of diabetes mellitus, especially Type II diabetes and hyperglycaemia and certain complications thereof, hyperlipidaemia, hypertension, cardiovascular disease, especially atherosclerosis and for treating certain eating disorders in a mammal such as a human, which method comprises administering per day 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form, to a mammal in need thereof.

Preferably, the method comprises the administration of 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 2 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 4 mg of Compound (I) in a pharmaceutically acceptable form.

Preferably, the method comprises the administration of 8 mg of Compound (I) in a pharmaceutically acceptable form.

No adverse toxicological effects have been established for the compositions or methods of the invention in the abovementioned dosage ranges.

The following example illustrate the invention but do not limit it in any way.

Example

Preparation of Concentrate: Tabletting concentrate was prepared using the following materials

Ingredient	Quantity (%)
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydoxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose (Avicel PH102)	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

The concentrate was then formulated into tablets using the following:

	Quantity (mg per Tablet)			
Tablet Strength	**1.0mg**	**2.0mg**	**4.0mg**	**8.0mg**
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose (Avicel PH102)	27.85	25.85	21.85	43.70
Lactose monohydrate, (Pharmatose DCL15),	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Opadry	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0